REMARKS

Applicant respectfully requests reconsideration. Claims 121-142 were previously pending in this application. Claims 121, 131 and 139-142 are amended. Support for these amendments can be found at least on page 7 lines 21-22, page 33 lines 10-13, page 102 lines 21-23, and in the sequence listing. No new matter has been added.

Claims 121-142 are pending for examination with claims 121 and 139-142 being independent claims.

Rejection under 35 U.S.C. §112

Enablement

Claims 121-124, 128-132 and 139-142 are rejected under 35 U.S.C. §112, first paragraph, enablement. The Examiner acknowledges that the specification enables "a method for treating cancer in a subject comprising administering the unmethylated immunostimulatory oligonucleotide of SEQ ID NO:246 comprising a modified backbone and a chemotherapeutic agent." However, the Examiner asserts that the specification does not enable a similar method using an oligonucleotide that lacks a phosphate backbone modification. Applicant respectfully traverses. The prior office action response provided a Wands analysis of the pending claims. The present response therefore deals specifically with the particular issues raised by the Examiner including the interpretation of "a nucleotide sequence", the length and sequence of the oligonucleotide, and the phosphate backbone modification.

Notwithstanding the Examiner's acknowledgement of what the specification enables (see quoted passage above), the Examiner interprets the recitation of "a nucleotide sequence of SEQ ID NO:246" to "require only the nucleotide sequence, or even a fragment of SEQ ID NO:246". Claims 121 and 139-142 are amended to clarify that the oligonucleotide in each claim encompasses at least the entire nucleotide sequence of 5' TCG TCG TTT TGT CGT TTT GTC GTT 3', and not (as the Examiner asserts) only that sequence or only a fragment of that sequence. Support for this amendment can be found throughout the specification including page 7 lines 28-32 (i.e., "the CpG oligonucleotide has a sequence selected from the group consisting of SEQ ID NO: .... 246").

Moreover, Applicant has amended claims 121 and 139-142 to recite that the C in each recited CG dinucleotide of SEQ ID NO:246 is unmethylated. Support for this amendment can be found throughout the specification including page 7 lines 21-22 and in the description of SEQ ID NO:246 in the sequence listing.

The Examiner further asserts that the specification does not enable oligonucleotides that contain sequence in addition to that of SEQ ID NO:246. The Examiner argues that "(T)here is no basis or objective evidence that the inclusion of additional nucleotides or sequences to SEQ ID NO:246 would function equivalently, particularly in view of the prior art and applicant's specification which show that both length and nucleotide content are factors in determing (sic) the immunostimulatory properties of a given CpG oligonucleotide." This statement however is unsubstantiated to the extent that the Examiner did not cite the prior art providing such teaching. The Examiner is requested to identify the prior art referred to before Applicant can fully respond to this assertion. With respect to the teaching in the specification itself, Applicant notes that the specification teaches that increasing length of a T-rich oligonucleotide up to 30 nucleotides results in increased immunostimulatory activity and that increasing length beyond 30 nucleotides had no further effect (including no diminished effect). With respect to the effect of sequence on the immunostimulatory activity of oligonucleotides, Applicant notes that the specification does not teach that the immunostimulatory activity of SEQ ID NO:246 is abolished by flanking sequences. To the contrary, the specification teaches that adding poly A or poly T stretches to the nucleotide sequence of SEQ ID NO:246 actually increases its immunostimulatory activity. (See page 31, lines 11-15.) Addition of G residues to the sequence reduced but did not abolish its activity.

The Examiner further asserts that the claimed method is not enabled if the oligonucleotide does not have a modified backbone. Applicant respectfully traverses. The specification teaches that oligonucleotides can have unmodified or modified backbones. The specification further teaches that in some instances modified backbones may be preferred due to their ability to increase the half-life of the oligonucleotide in vivo. However, the specification does not teach that oligonucleotides lacking backbone modifications are not immunostimulatory. To the contrary, the specification contemplates that phosphodiester backbone oligonucleotides can be used as is or in one of a number of formulations, known in the art, to enhance their

immunostimulatory effect. (See for example page 2, lines 2-5 citing Yamamoto et al. 1994 Microbiol. Immunol. 38:831-836, and Gramzinski et al. 1998 Mol. Med. 4:109-118.) Applicant previously provided the Examiner with a number of references that describe immunostimulation by nucleic acids having phosphodiester (i.e., unmodified backbones) in animal tumor models. (See Dow et al. J. Immunol, 1999, 163, 1552-1561; Rudginsky et al. Molecular Therapy, 2001, v. 4, 347-355; Siders et al. Molecular Therapy, 2002, v. 6, p.519-527; and Lanuti et al. Cancer Research, 2000, v. 60, p. 2955-2963.) The Examiner has not addressed these references and is asked to do so.

In view of the foregoing, Applicant maintains that the claimed method is enabled in view of the teaching in the specification and the knowledge and skill in the art at the time of filing. Reconsideration and withdrawal of this rejection is respectfully requested.

Written Description

Claims 121-142 are rejected under 35 U.S.C. §112, first paragraph, written description. The Examiner considers that the rejected claims introduce new matter that was not described in the specification. For example, the Examiner asserts that the specification does not provide written description for oligonucleotides that comprise the nucleotide sequence of SEQ ID NO:246, and the combination of such oligonucleotides with the specifically claimed chemotherapeutic agents. Applicant respectfully traverses.

With respect to the genus of claimed oligonucleotides, possession of a claimed invention can be shown by the disclosure of a structural chemical formula, and an invention can be shown to be complete by the disclosure of "sufficiently detailed, relevant identifying characteristics" that in the case of a biomolecule include its sequence. MPEP 2163(I). Applicant maintains that the specification demonstrates possession of the claimed oligonucleotide genus by providing the 24 nucleotide consensus sequence that identifies (and thus is common to) all members of the claimed genus. The specification explicitly contemplates the claimed genus of oligonucleotides, contrary to the Examiner's position that "the present application does not name or describe the subgenus of immunostimulatory sequences that "comprise" SEQ ID NO:246". (See page 19 lines 6-9 and 30-31 which state, inter alia, "wherein the CpG nucleic acid has a nucleotide sequence comprising SEQ ID NO:246)." The specification further teaches that other species in

the genus are immunostimulatory. (See for example page 31 lines 11-15 which teach that oligonucleotides having the sequence of SEQ ID NO:246 and a poly A or a poly T tail are immunostimulatory.) Additional species of the claimed genus are provided by the specification including SEQ ID NOs: 262, 273, 300, 305, 352, 412, 413, 429 and 891. These species vary with respect to length, flanking sequence, and backbone content, yet all comprise the complete nucleotide sequence of SEQ ID NO:246 and all are taught by the specification to be immunostimulatory. With respect to the effect of length on the immunostimulatory activity of the claimed genus, Applicant reiterates that the specification teaches that increasing length of a T-rich oligonucleotide to 30 nucleotides actually increases its immunostimulatory activity and that increases beyond 30 nucleotides do not diminish this activity.

The Examiner cites Enzo Biochem and Noelle v. Lederman for the proposition that "the disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute a gen[us]." As stated above, the instant specification provides more than one species within the claimed genus and thus the reliance on Enzo and Noelle is misplaced.

The Examiner takes issue with Applicant's rebuttal that "one of ordinary skill in the art could envision additional species within the recited genus" stating that the rebuttal appears to address an enablement rather than written description rejection. Applicant respectfully points the Examiner to MPEP 2163(I)(A) where it is stated that "(A) lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed ..." (citing Fujikawa v. Wattanasin and In re Ruschig). Applicant's point was that one of ordinary skill in the art would be able to readily envisage the genus of oligonucleotides of the claimed invention and thus the genus was adequately described. The Examiner further asserts that the combination of the claimed oligonucleotide genus with any of carboplatin, paclitaxel, doxorubicin, cisplatin or gemcitabine is not supported by the specification. While the Examiner has identified at least one passage in the specification that describes the combination of an immunostimulatory nucleic acid with an anti-cancer therapy that can be carboplatin, paclitaxel, doxorubicin, cisplatin or gemcitabine, the Examiner does not consider this to be sufficient disclosure of the claimed method. Respectfully, the cited passage adequately describes the use of an immunostimulatory nucleic in combination

with any of the recited anti-cancer therapies. Carboplatin, paclitaxel, doxorubicin, cisplatin and gemcitabine are explicitly recited in the specification. The specification therefore provides adequate support for the combination of immunostimulatory nucleic acids with each of these anti-cancer therapies.

The specification also emphasizes the use of the claimed oligonucleotides with anti-cancer therapies. (See for example page 19 lines 6-9 which specifically identify "a CpG nucleic acid, wherein the CpG nucleic acid has a nucleotide sequence comprising SEQ ID NO:246" to be used in combination with an anti-cancer therapy.) The specification emphasizes the immunostimulatory activity of SEQ ID NO:246, including activity that correlates with anti-tumor activity in vivo. (See for example page 19 lines 6-9 and 30-31, page 25 lines 29-31, page 31 lines 11-15, page 32 lines 4-5, page 128 lines 8-9 and 20-23, page 135 lines 6-8 and 20-22, page 137 lines 3-16, page 139 lines 5-8, and FIGs. 4-10.)

Claim 131 has been amended to recite that the subject is administered another cancer medicament. Support for this amendment can be found on page 102 lines 21-23. The specification further teaches that a cancer medicament can be a chemotherapeutic agent. (See page 102 lines 9-12.)

The specification clearly, specifically and adequately describes the claimed methods including the specific combinations of oligonucleotides and anti-cancer therapies. One of ordinary skill in the art would have recognized that Applicant had possession of the claimed invention. Reconsideration and withdrawal of this rejection is respectfully requested.

Rejection under 35 U.S.C. §103

Claims 121-142 are rejected under 35 U.S.C. §103(a) as being unpatentable over Wagner et al (US 2004/0235778) in view of Maxwell et al. (Seminars in Oncology Nursing, 8(2):113-123, May 1992).

The pending claims relate to a method for increasing the responsiveness to a cancer therapy comprising administering an oligonucleotide that comprises the nucleotide sequence of SEQ ID NO:246 and the specific cancer therapy in an effective amount. Claim 131 recites that two cancer therapies are administered to the subject. Neither the primary nor the secondary

references teach the limitation of "increasing the responsiveness to a cancer therapy" by using the claimed oligonucleotides.

The combination of references does not render obvious the pending claims at least because the combination of references does not teach each and every limitation of the pending claims.

Moreover, the Examiner's rationale for combining the references in the first instance related to the ability of immunostimulatory nucleic acids to stimulate hematopoiesis and the teaching of myelosuppression by certain chemotherapeutic agents. Applicant notes however that when CpG oligonucleotides were used with chemotherapy, as described in Manegold et al., adverse events of thrombocytopenia and anemia were more common than when chemotherapy was used alone.

Finally, in the present office action, the Examiner pointed to Table 2 of Manegold et al. and concluded that it showed that the combined use of the oligonucleotide with paclitaxel and carboplatin had a 36% response rate while paclitaxel and carboplatin without the oligonucleotide had a 49% response rate. Applicant wishes to clarify for the record that Table 2 of the reference indicates the percentage of subjects receiving particular treatments. Table 2 shows that 36% of subjects that received the oligonucleotide also received carboplatin and paclitaxel, and that 49% of the subjects that did not receive the oligonucleotide received carboplatin and paclitaxel. The responses to the various treatment regimens are detailed in Figs. 3 and 4. Thus, the reference does not support the conclusion drawn by the Examiner. Applicant however brings to the Examiner's attention the reference cited to the Office in an Information Disclosure Statement mailed July 20, 2007.

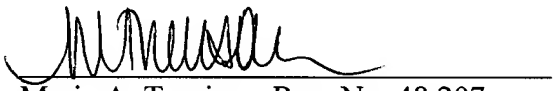
Reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,



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